# Synopsis – Study 12710A

**Study Title**

Interventional, randomized, double-blind, placebo-controlled, active-reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 12 to 17 years, with Major Depressive Disorder (MDD)

**Investigators**

118 principal investigators at 118 sites in 19 countries

*Signatory investigator* – [redacted]

**Study Sites**

118 sites – 2 in Bulgaria, 1 in Canada, 4 in Columbia, 1 in Estonia, 3 in France, 5 in Germany, 2 in Hungary, 5 in Italy, 3 in the Republic of Korea, 4 in Latvia, 7 in Mexico, 7 in Poland, 16 in Russia, 5 in Serbia, 1 in South Africa, 5 in Spain, 4 in Ukraine, 2 in United Kingdom, and 41 in United States

**Publications**

None (as of the date of this report)

**Study Period**

*First patient first visit* – 3 June 2016 (the date when the first *Informed Consent Form* was signed)

*Last patient last visit* – 30 July 2019 (the date of the last protocol-specified contact with any patient)

**Objectives and Endpoints**

| **Objectives** | **Endpoints** |
|---|---|
| *Primary Objective* | *Primary Endpoint* |
| • to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo after 8 weeks of treatment on depressive symptoms in adolescents with a DSM-5® diagnosis of MDD | • depressive symptoms<br>– Δ Children's Depression Rating Scale – Revised version (CDRS-R) total score to Week 8 |
| *Secondary Objectives* | *Secondary Endpoints*[a] |
| • to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo during the 8 weeks of treatment on:<br>– cognitive performance<br>– clinical global impression (CGI)<br>– functionality<br>– health-related quality of life | • depressive symptoms<br>– Δ CDRS-R total score<br>– Δ CDRS-R *Mood* (4 items), *Somatic* (6 items), *Subjective* (4 items), and *Behaviour* (3 items) subscores<br>– CDRS-R response[b]<br>– CDRS-R remission (defined as a CDRS-R total score ≤28)<br>– Δ General Behaviour Inventory (GBI) Depression subscale score, using the 10-item depression subscale, assessed by parent (PGBI-10D) and child (CGBI-10D)<br>– Parent Global Assessment – Global Improvement (PGA) score<br>• cognitive performance<br>– Δ Symbol Digit Modalities Test (SDMT) (number of correct responses) |

Δ = change from Randomization

a At each visit assessed during the DB Period

b Defined as a ≥50% decrease in CDRS-R total score, calculated as:
(change from baseline [Randomization]) / (baseline value – 17)

| **Objectives and Endpoints (continued)** | |
|---|---|
| **Objectives** | **Endpoints** |
| *Secondary Objectives* | *Secondary Endpoints*[a] |
| | • global clinical impression<br>– Δ CGI – Severity of Illness (CGI-S) score<br>– CGI – Global Improvement (CGI-I) score<br>– CGI-S remission (defined as a CGI-S score of 1 or 2)<br>• functionality<br>– Δ Children's Global Assessment Scale (CGAS) score<br>– Δ Pediatric Quality of Life Inventory (PedsQL™) Visual Analogue Scales (VAS) score in each of the 6 domains<br>– Δ PedsQL™ VAS average score in each of the 6 domains<br>– Δ PedsQL™ VAS *Emotional Distress* summary score<br>• health-related quality of life<br>– Δ Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) total score (items 1 to 14)<br>– Δ PQ-LES-Q *Overall Evaluation* score (item 15) |
| • to assess pharmacokinetics of vortioxetine in paediatric patients aged 12 to 17 years using a population pharmacokinetic approach | • pharmacokinetics<br>– pharmacokinetic (PK) parameters for vortioxetine and fluoxetine |
| *Exploratory Objective* | *Exploratory Endpoints* |
| • to explore the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo on co-morbid symptoms | • depressive symptoms<br>– Δ CDRS-R item scores<br>• co-morbid symptoms<br>– Δ Multidimensional Anxiety Scale for Children short version (MASC-10) total score |
| *Safety Objective* | *Safety Endpoints* |
| • to evaluate the safety and tolerability of vortioxetine 10 mg/day and 20 mg/day *versus* placebo in adolescents with a DSM-5® diagnosis of MDD | • adverse events (AEs)<br>• tolerability was also assessed using the Paediatric Adverse Event Rating Scale (PAERS)<br>• absolute values and Δ in clinical safety laboratory tests, vital signs, weight, height, and electrocardiogram (ECG) parameters<br>• potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values<br>• Columbia Suicide Severity Rating Scale (C-SSRS) scor<br>• Δ GBI Mania subscale score, using the 10-item Mania subscale, assessed by parent (PGBI-10M) and child (CGBI-10M) |
| Δ = change from Randomization | |
| a At each visit assessed during the DB Period | |

**Study Methodology**

- This was an interventional, prospective, multi-national, multi-site, randomized, two-period, single- and double-blind, parallel-group, placebo-controlled, active-reference (fluoxetine), fixed-dose study.
- The study consisted of:
  - Screening Period – 5 to 15 days
  - Single-blind (SB) Period – 4-week single-blind (patients and parents) period of treatment with standardized brief psychosocial intervention (BPI) and placebo
  - Double-blind (DB) Period – 8-week double-blind period of treatment with BPI and placebo, vortioxetine 10 mg/day, vortioxetine 20 mg/day, or fluoxetine 20 mg/day
  - Safety Follow-up Period – 4-week period after completion of the study or after withdrawal from the study; this procedure did not apply to patients who entered the open-label extension study (Study 12712A)
- Patients who fulfilled the Randomization criteria for incomplete improvement in depressive symptoms at the end of the SB Period (Week 4) entered the DB Period. Incomplete improvement was defined as a <40% decrease in CDRS-R total score from Enrolment, CDRS-R total score ≥40, and a PGA score >2. The patients were randomized 1:1:1:1 to 8 weeks of double-blind treatment with vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine 20 mg/day, or placebo. Patients who did not fulfill the Randomization criteria were withdrawn from the study before Week 4 and, as a rescue procedure, these patients were offered up to four outpatient visits to the study site for consultations.

**Number of Patients Planned**

600 patients were planned for randomization with 150 patients in each treatment group

**Diagnosis and Main Selection Criteria**

Outpatients with a primary diagnosis of MDD according to DSM-5® and confirmed using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version (K-SADS-PL) criteria, who:

- had a CDRS-R total score ≥45 at the Screening Visit and at Enrolment
- had a CGI-S score ≥4 at the Screening Visit and at Enrolment
- were a boy or a girl ≥12 and ≤17 years of age

To be included in the DB Period, the patients:

- had to have a CDRS-R total score ≥40 at the Week 3 Visit and Week 4 Visit in the SB Period
- had to have a <40% decrease in CDRS-R total score (subtracted by 17 to avoid a flooring effect) compared to Enrolment at the Week 3 Visit and Week 4 Visit in the SB Period
- had to have a PGA score >2 at the Week 3 Visit and Week 4 Visit in the SB Period

**Investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers**

*Vortioxetine* – 10 or 20 mg/day; encapsulated tablets, orally; batch Nos. E144509-0006E, E144509-0051E, E144509-0077E, P144509-0016E, P144509-0036E, P144509-0058E (5 mg); batch Nos. E144509-0002E, E144509-0054E, E144509-0078E, P144509-0017E, P144509-0037E, P144509-0059E (10 mg); batch Nos. E144509-0003E, E144509-0052E, E144509-0079E, P144509-0018E, P144509-0038E, P144509-0060E (15 mg); batch Nos. E144509-0004E, E144509-0053E, E144509-0080E, P144509-0019E, P144509-0039E, P144509-0061E (20 mg)

**Reference Therapy, Doses and Mode of Administration, Batch Numbers**

*Placebo* – capsules, orally; batch Nos. E144509-0005E, E144509-0076E, P144509-0010E, P144509-0033E, P144509-0075E

*Fluoxetine* – 20 mg/day; encapsulated tablets or capsules, orally; batch Nos. E144509-0007E, E144509-0055E, E144509-0081E, P144509-0011E, P144509-0034E, P144509-0062E (10 mg); batch Nos. E144509-0008E, E144509-0056E, E144509-0082E, P144509-0012E, P144509-0035E, P144509-0063E (20 mg)

**Duration of Treatment**

12 weeks – SB Period: 4 weeks; DB Period: 8 weeks

**Statistical Methodology**

- The following analysis sets were used:
  - *all-patients enrolled set* (APES) – all patients enrolled
  - *all-patients-treated set* (APTS_A) – all patients in the APES who took at least one dose of single-blind investigational medicinal product (IMP)
  - *all-patients-randomized set* (APRS) – all patient randomized
  - *all-patients-treated set* (APTS) – all randomized patients who took at least one dose of double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid assessment at Randomization and at least one valid post-Randomization assessment of the CDRS-R total score
- Unless otherwise indicated, the efficacy analyses were based on the FAS, the safety analyses for the SB Period were based on the APTS_A, and the safety analyses for the DB Period were based on the APTS.
- The change from Randomization in CDRS-R total score at Week 8 was analysed using a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM). The model included the fixed, categorical effects of treatment, country, and week and the continuous covariates of CDRS-R total score at Randomization, treatment-by-week interaction, and CDRS-R at Randomization-by-week interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.
- The primary comparison was the average effect of the two vortioxetine (Avg. VOR) doses *versus* placebo at Week 8 in the DB Period based on the *SAS lsmestimate statement*. The testing strategy also included comparisons of the individual vortioxetine doses *versus* placebo. First, the comparison of the average effect of the two vortioxetine doses *versus* placebo was tested at a two-sided 5% significance level. If the result was statistically significant, each vortioxetine dose was tested separately *versus* placebo at a two-sided 5% significance level. Statistical significance could be claimed on the individual doses only if significance was claimed for the average vortioxetine doses.
- Sensitivity analyses were performed using:
  - a pattern-mixture model
  - an analysis of covariance (ANCOVA) model by visit using both the last observation carried forward (LOCF) and observed cases (OC), including country and treatment
- An analysis based on an MMRM model similar to the one used in the primary analysis was performed after removing patients in the vortioxetine and fluoxetine groups where PK indicated that the patients had not taken IMP in the DB Period.
- Continuous secondary endpoints were analysed using an MMRM model similar to the one specified for the primary endpoint with comparisons from the same model used for all time points. In addition, ANCOVA (OC and LOCF) was performed per visit with treatment and country as factors and score at Randomization as a covariate.
- For dichotomous outcomes, the primary methodology for analysis at each week during DB Period (FAS, LOCF) was logistic regression with treatment as a factor and the score at Randomization as a covariate. This was supplemented by a similar analysis based on OC. In additional sensitivity analyses, patients with a missing value at the week analysed were classified as non-responders/non-remitters. The same logistic regression was applied for both classifications.
- The exploratory endpoints were analysed using an MMRM model similar to the one specified for the primary endpoint. In addition, ANCOVA (OC and LOCF) were performed with treatment and country as factors and the score at Randomization as a covariate.
- The population PK (popPK) of vortioxetine was determined using nonlinear mixed effect modelling using NONMEM®. The first-order conditional error with interaction minimization method was used. The structural popPK model used was the one developed in a previous pooled popPK analysis in healthy adult subjects, which is a two-compartment model with lag-time and with first-order absorption and elimination.
- Compliance was based on patient reporting and was defined as the percentage of IMP taken as planned.

**Statistical Methodology (continued)**

- Compliance was also assessed using plasma concentration data for fluoxetine and vortioxetine. Plasma drug concentrations below the detection limit lower limit of quantification (<LLOQ) and unrealistically low plasma drug concentrations (estimated oral clearance >120L/h) estimated from the popPK analysis (vortioxetine) compared to those observed historically in healthy adult subjects treated under well-controlled conditions were used in this assessment.
- The overall incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal for the SB Period and DB Period were summarized by primary system organ class (SOC) and preferred term.
- Adverse events, clinical safety laboratory test vlues, vital signs, body measurements (height, weight, body mass index [BMI]), ECG parameters, and C-SSRS scores were summarized using descriptive statistics.

**Patient Disposition and Analysis Sets**

- 1035 patients were screened
- Patient disposition for the SB Period is summarized below:

| | PBO | |
|---|---|---|
| | **n** | **(%)** |
| **Patients enrolled (APES)** | 784 | |
| **Patients treated (APTS A)** | 777 | |
| Patients completed | 616 | 79.3 |
| Patients withdrawn | 161 | 20.7 |
| **Primary reason for withdrawal** | | |
| Failure to meet randomization criteria | 103 | 13.3 |
| Adverse events | 12 | 1.5 |
| Lack of efficacy | 7 | 0.9 |
| Non-complince with IMP | 2 | 0.3 |
| Protocol violation | 4 | 0.5 |
| Withdrawal of consent | 12 | 1.5 |
| Lost to follow-up | 7 | 0.9 |
| Other | 14 | 1.8 |

PBO = placebo

- Patient disposition for the DB Period is summarized below:

| | PBO | | VOR 10 mg | | VOR 20 mg | | FLU | |
|---|---|---|---|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| **Patients randomized (APRS)** | 154 | | 147 | | 162 | | 153 | |
| **Patients treated (APTS)** | 154 | 100 | 147 | 100 | 161 | 100 | 153 | 100 |
| Patients completed | 138 | 89.6 | 126 | 85.7 | 140 | 87.0 | 138 | 90.2 |
| Patients withdrawn | 16 | 10.4 | 21 | 14.3 | 21 | 13.0 | 15 | 9.8 |
| **Primary reason for withdrawal** | | | | | | | | |
| Adverse events | 2 | 1.3 | 4 | 2.7 | 8 | 5.0 | 5 | 3.3 |
| Lack of efficacy | 2 | 1.3 | 3 | 2.0 | 0 | | 1 | 0.7 |
| Non-compliance with IMP | 0 | | 1 | 0.7 | 4 | 2.5 | 1 | 0.7 |
| Protocol violation | 2 | 1.3 | 1 | 0.7 | 0 | | 0 | |
| Withdrawal of consent | 1 | 0.6 | 2 | 1.4 | 2 | 1.2 | 2 | 1.3 |
| Lost to follow-up | 2 | 1.3 | 4 | 2.7 | 2 | 1.2 | 0 | |
| Other | 7 | 4.5 | 6 | 4.1 | 5 | 3.1 | 6 | 3.9 |
| **Analysis sets** | | | | | | | | |
| Full-analysis set (FAS) | 153 | | 145 | | 159 | | 150 | |

FLU = fluoxetine; PBO = placebo; VOR = vortioxetine

**Demographics and Baseline Characteristics of the Study Population**

*Randomized Patients*

- Demographics were comparable across treatment groups: the mean age of the patients was 15 years and the majority (approximately 71%) were White. The mean height, weight, and BMI at Randomization were 165 cm (ranging from 140 to 198 cm), 63.6 kg (ranging from28 to 153 kg), and 23.2 kg/m$^2$ (ranging from 13.1 to 56.7 kg/m$^2$), respectively.
- Overall, the demographics, height, weight, and BMI at Randomization for the patients in the APTS were similar to what was seen at Enrolment for the patients in the APTS_A.
- At Enrolment, the majority of the adolescents were pubertal (Tanner stage II to IV: 73% of the girls and 80% of the boys) or post-pubertal (Tanner stage V: 25% of the girls and 14% of the boys). The majority (>93%) of the patients did not smoke or drink alcohol.
- At Enrolment, the patients in the APTS_A had a mean CDRS-R total score of 64.5 points (ranging from 45 to 97 points) and a mean CGI-S score of 5.0 points (ranging from 4 to 7 points) (corresponding to *markedly ill*).
- At Randomization, the patients in the APTS had a mean CDRS-R total score of 62 points (ranging from 40 to 87 points) and a mean CGI-S score of 4.8 points (ranging from 3 to 7 points) (corresponding to *markedly ill)*.

**Efficacy Results**

- The primary efficacy results are summarized below (FAS, MMRM):

| Endpoint | N | Mean | Treatment Difference to PBO (95% CI) | p-value |
|---|---|---|---|---|
| **Δ CDRS-R total score at Week 8** | | | | |
| PBO | 137 | -18.22 | | |
| Avg. VOR | | -18.01 | 0.21 (-2.41; 2.82) | 0.8778 |
| VOR 10 mg | 126 | -17.09 | 1.13 (-1.94; 4.20) | 0.4702 |
| VOR 20 mg | 139 | -18.94 | -0.72 (-3.71; 2.27) | 0.6373 |
| FLU 20 mg | 137 | -21.95 | -3.73 (-6.74; -0.72) | 0.0152 |

FLU = fluoxetine; PBO = placebo; VOR = vortioxetine

- In the primary efficacy analysis, the mean change from Randomization to Week 8 in CDRS-R total score was -18 points for both placebo and Avg. VOR and the difference (0.2 points in favour of placebo) was not statistically significant (p = 0.9). The testing strategy stopped at this step.
- In the analyses of the mean change from Randomization to Week 8 in CDRS-R total score for the individual vortioxetine doses (10 and 20 mg/day) *versus* placebo, the nominal p-value was >0.05 for both doses.
- In the fluoxetine group, the mean change from Randomization to Week 8 in CDRS-R total score was -22 points and the difference to placebo was -3.7 points with a nominal p-value at 0.015 (<0.05), thus validating the study's assay sensitivity for efficacy.
- In general, the results of the secondary and exploratory efficacy analyses were consistent with those of the primary efficacy analysis.

**Pharmacokinetic Results**

- Vortioxetine steady-state exposures in adolescents were similar to those previously reported in adults both for vortioxetine 10 and 20 mg. Non-compliance based on PK information was 11% in the vortioxetine 10 mg group, 20% in the vortioxetine 20 mg group, and 14% in the fluoxetine group.

**Safety Results**

- The adverse event incidence is summarized below for the DB Period:

| | PBO | | VOR 10 mg | | VOR 20 mg | | FLU 20 mg | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Patients treated | 154 | | 147 | | 161 | | 153 | |
| Patients with treatment-emergent SAEs | 1 | 0.6 | 4 | 2.7 | 7 | 4.3 | 3 | 2.0 |
| Patients with TEAEs | 63 | 40.9 | 69 | 46.9 | 95 | 59.0 | 75 | 49.0 |
| Patients with TEAEs leading to withdrawal | 2 | 1.3 | 4 | 2.7 | 9 | 5.6 | 5 | 3.3 |
| Total number of treatment-emergent SAEs | 1 | | 4 | | 8 | | 3 | |
| Total number of TEAEs | 153 | | 204 | | 272 | | 202 | |
| Total number of TEAEs leading to withdrawal | 4 | | 4 | | 15 | | 5 | |

FLU = fluoxetine; PBO = placebo; VOR = vortioxetine

- The TEAEs with an incidence ≥5% in any treatment group are summarized by preferred term below:

| Preferred Term | PBO | | VOR 10 mg | | VOR 20 mg | | FLU 20 mg | |
|---|---|---|---|---|---|---|---|---|
| (MedDRA Version 21.0) | n | (%) | n | (%) | n | (%) | n | (%) |
| Patients treated | 154 | | 147 | | 161 | | 153 | |
| Nausea | 7 | 4 5 | 21 | 14.3 | 31 | 19.3 | 10 | 6.5 |
| Headache | 12 | 7.8 | 23 | 15.6 | 20 | 12.4 | 10 | 6.5 |
| Vomiting | 1 | 0.6 | 7 | 4.8 | 15 | 9.3 | 8 | 5.2 |
| Nasopharyngiitis | 5 | 3.2 | 6 | 4.1 | 10 | 6.2 | 10 | 6.5 |
| Diarrhoea | 5 | 3.2 | 5 | 3.4 | 9 | 5.6 | 7 | 4.6 |
| Dizziness | 5 | 3.2 | 11 | 7.5 | 7 | 4.3 | 6 | 3.9 |

- In the DB Period, the incidences of TEAEs, SAEs, and TEAEs leading to withdrawal were higher in the vortioxetine and fluoxetine groups than in the placebo group, with the highest incidences in the vortioxetine 20 mg group.
- In general, the incidences of the TEAEs with an incidence ≥5% were higher in the vortioxetine and fluoxetine groups than in the placebo group, in particular for *nausea*, *headache*, and *vomiting*.
- The only *severe* TEAEs that occurred in >1 patient in any treatment group were *suicidal ideation* (4 patients: 1 in the vortioxetine 10 mg group and 3 in the vortioxetine 20 mg group) and *headache* (2 patients: both in the vortioxetine 10 mg group).
- Two deaths were reported: 1 patient committed suicide in the Screening Period, and 1 patient (from the placebo group) committed suicide approxmiately 1 year after completing the study.
- A total of 15 patients had SAEs in the DB Period, 7 of which occurred in the vortioxetine 20 mg group. Only *suicidal ideation* (6 patients) occurred in >1 patient in any treatment group.
- Two pregnancies were reported: 1 in the Screening Period and 1 (in the vortioxetine 10 mg group) in the DB Period; the *outcome* of that pregnancy is not known.
- In the SB Period, 13 patients had suicide-related TEAEs captured using Standadized MedDRA Queries (SMQ) *Suicide/Self-injury*. *Suicidal ideation* (7 patients), *intentional overdose* (3 patients), *intentional self-injury* (3 patients), and *suicidal attempt* (2 patients) were the suicide-related TEAEs that occurred in >1 patient in the SB Period. For 8 of these patients, at least 1 of the TEAEs was reported as an SAE.
- In the DB Period, 14 patients had suicide-related TEAEs captured using the SMQ *Suicide/Self-injury*; the TEAEs were reported for 2 patients in the vortioxetine 10 mg and 6 patients each in the vortioxetine 20 mg and fluoxetine groups. *Suicidal ideation* (8 patients: 1 in the vortioxetine 10 mg group, 4 in the vortioxetine 20 mg group, and 3 in the fluoxetine group) and *intentional self-injury* (4 patients: 1 in the vortioxetine 10 mg group, 2 in the vortioxetine 20 mg group, and 1 in the fluoxetine group) were the suicide-related TEAEs that occurred in >1 patient in the DB Period. For 6 of the 14 patients with suicide-related TEAEs, at least 1 of the TEAEs (*suicidal ideation* [6 patients] and *suicide attempt* [1 patient]) was reported as an SAE, all of which occured after more than 14 days of treatment.

**Safety Results (continued)**

- In the DB Period, 20 patients had TEAEs leading to withdrawal. *Suicidal ideation* (6 patients: 1 in the vortioxetine 10 mg group, 3 in the vortioxetine 20 mg group, and 2 in the fluoxetine group), *nausea* (3 patients: 1 in the vortioxetine 10 mg group and 2 in the vortioxetine 20 mg group), and *vomiting* (2 patients: both in the vortioxetine 20 mg group) occurred in >1 patient in the DB Period.
- The mean changes from Randomization in all the clinical safety laboratory tests; vital signs; weight, BMI, and height; and ECG parameters were small and comparable between treatment groups and not clinically relevant. Overall, the proportions of patients with post-Randomization PCS values for these variables were low and similar across treatment groups. The shift data indicate that the majority of the post-Randomization PCS laboratory values in >3 patients were already PCS at Randomization.
- In the DB Period, the proportions of patients with elevated liver enzymes were low and none of the elevated liver enzymes met the criteria of Hy's law.
- On the PAERS, the most common symptoms reported at Randomization were related to MDD (such as items related to *depressed mood*, *irritability*, and *fatigue*) or comorbid psychiatric conditions. The scores for the items related to MDD generally decreased over time and reflected the improvements captured by the efficacy scales in the respective treatment groups. The symptoms showing worsening compared to Randomization reflected the pattern of adverse events reported in this study, such as *nausea*, *vomiting*, and *hypersomnia*.
- During the study, based on the C-SSRS, the proportions of patients with no suicidal ideation or behaviour were similar to what was seen at Randomization. Two patients had suicidal behaviour (1 patient in the vortioxetine 20 mg group [*non-fatal suicide attempt*] and 1 patient in the fluoxetine group [*active suicidal ideation with specific plan and intent*]).
- Overall, the mean changes from Randomization to Week 8 in GBI Mania subscale score, as assessed by the parent or child, were small as were the differences to placebo (<0.4 points as judged by the parents and <0.6 points as judged by the children) and not clinically relevant. A GBI Mania subscale score ≥18 points, indicating a potential risk of mania, was reported only sporadically, with no clinically relevant difference across treatment groups. None of the scores ≥18 points were considered clinically significant by the investigator and none were reported as adverse events.

**Conclusions**

- In the primary efficacy analysis, the average of the two vortioxetine doses (10 and 20 mg) was not statistically significantly different to placebo based on the change from Randomization to Week 8 in CDRS-R total score in adolescents with MDD.
- In the analyses of the mean change from Randomization to Week 8 in CDRS-R total score for the individual vortioxetine doses (10 and 20 mg/day) *versus* placebo, the nominal p-value was >0.05 for both doses.
- In the corresponding analysis for fluoxetine, the active reference in this study, the nominal p-value was <0.05, thus validating the study's assay sensitivity for efficacy.
- In general, the results of the secondary and exploratory efficacy analyses were in line with those of the primary efficacy analyses.
- Vortioxetine exposures based on PK data in adolescents were similar to those previously reported in adults.
- Vortioxetine was generally safe and well tolerated in adolescents with MDD. The safety and tolerability profile of vortioxetine in adolescents was comparable to what has been observed in clinical studies of vortioxetine in adults with MDD.

**Report Date**

27 May 2020 (Amendment 1), 17 December 2019 (Clinical Study Report)

This study was conducted in compliance with *Good Clinical Practice*.